Docket Number	CT-2709 NP

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James Epperson	/james epperson/	January 30, 2007
Type or print name	Signature	Date

IN RE APPLICATION OF Boy et al.

APPLICATION NO: 10/731,854 EXAMINER: Patricia Morris

FILED: 12/09/2003 ART UNIT: 1625

FOR: 2-Aryl thiazole derivatives as KCNQ modulators

MAIL STOP: Amendments
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Appeal Brief filed under 37 CFR 41.37

Sir:

We received the Office Action dated September 28, 2006 which finally rejected the claims and set a three month shortened statutory response period ending December 28, 2006. In response, the appellants filed a timely notice of appeal on December 14, 2006 and now submit the following appeal brief. Please charge deposit account 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $500 for payment of the fee under 37 CFR 41.20(b)(2).

Respectfully submitted,

Date: January 30, 2007

/james epperson/

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

James Epperson
Agent for Appellants
Reg. No. 52,867
Phone: (203) 677-6974

(i) Real party of interest. Bristol-Myers Squibb Company is the real party of interest. Bristol-Myers Squibb is located at 345 Park Avenue, New York, NY, 10154-0037. The inventors assigned the entire interest by virtue of an assignment executed and recorded on January 9, 2004 (reel/frame 014245/0530).

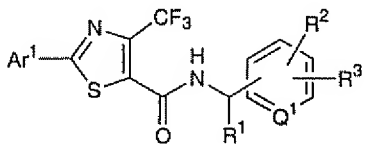
(ii) Related appeals and interferences. There are no related appeals or interferences.

(iii) Status of the Claims Claims 1 and 3-17 are pending. Claim 2 has been cancelled. Claims 12-17 were withdrawn from consideration by the examiner. Claims 1 and 3-11 were rejected under 35 USC 103(a).

(iv) Status of amendments. There are no pending amendments.

(v) Summary of claimed subject matter. The claims encompass a series of 2-aryl thiazole compounds (see generic Markush structure below). Independent claim 1 encompasses all other claims. The subject matter defined in independent claim 1 is disclosed in the specification beginning at page 3, line 15.

The compounds are openers of certain potassium channels termed KCNQ channels. By modulating these ion channels, the compounds affect the polarization of neuronal cells and may benefit those afflicted with abnormal neuronal firing, for example, those afflicted with migraine pain. The claims also encompass pharmaceutical compositions and methods of treatment using these compounds.



(vi) Grounds for rejection to be reviewed on appeal. Claims 1 and 3-11 stand rejected as obvious under 35 USC 103(a) over Akiyoshi (Japanese Patent Application no. 1990-249254) in view of Sierra (US patent 6,518, 290).

(vii) Argument.

Rejection under 35 USC 103 over Akiyoshi (Japanese Patent Application no. 1990-249254) in view of Sierra (US patent 6,518, 290).

Claims 1, 3-11.

Summary. The examiner has combined two reference articles which disclose certain compounds that share some but not all structural characteristics and do not share any common property and used this combination to allege that the claimed compounds are obvious. The appellants argue (1) that because the references do not share any common property and are structurally distinct, there is no reason for those skilled in either art to combine the references and (2) when combined, the artisan must pick and choose variables selectively and without regard to the biological properties of the compounds.

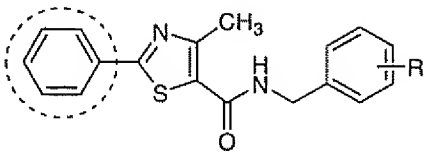
The test for obviousness. Obviousness is determined after evaluating the four factual inquiries laid out in *Graham v. John Deere* 383 US 1, 148 USPQ 459 (1966): (1) determine the scope and content of the prior art, (2) ascertain the differences between the prior art and the claims, (3) resolve the level of ordinary skill in the art, and (4) evaluate evidence of secondary considerations.

The initial burden is on the examiner to provide some indication of the desirability of doing what the inventor has done. MPEP 2143. In order to establish this prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the reference or in the art to make the claimed invention. Second, there must be a reasonable expectation of success. Third, the prior art reference must teach all of the claim limitations. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

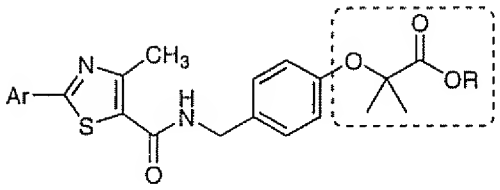
If the examiner does not establish a prima facie case of obviousness, there is no need for the appellants to bring forward any evidence of secondary considerations of obviousness. MPEP 2142. The appellants assert that the examiner did not establish a prima facie case of obviousness and therefore have not proffered any evidence of secondary considerations at this point.

The scope and content of the prior art. The examiner relies on Akiyoshi (Japanese Patent Application no. 1990-249254) in view of Sierra (US patent 6,518, 290).

Akiyoshi teaches a series of compounds having insecticidal activity (see table, p. 702, column 2). Examples 10 and 11 teach a phenyl substituent corresponding to Ar^1 in the claimed compounds (see structure below). Sierra teaches a series of compounds distinct from Akiyoshi and having human peroxisome proliferator activated receptor activity (PPAR). Sierra teaches 57 examples which all have a para substituted gem-dimethyl glycolic acid/ester moiety (see structure below, examples begin on column 30).



Akiyoshi Examples 10 and 11



Sierra: all 57 examples

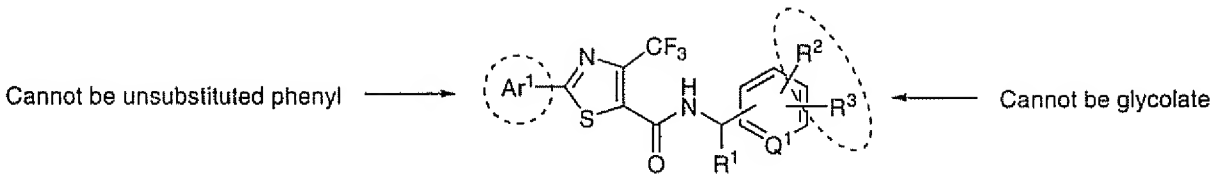
The appellants dispute that the references are properly combinable. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Akiyoshi teaches compounds with insecticidal activity; Sierra teaches compounds with PPAR activity. The references do not share any common property. Therefore, those skilled in the insecticidal art have no reason to expect that incorporating the structural features disclosed for PPAR activity would lead to insecticidal activity and likewise those skilled in the PPAR art would have no reason to expect that compounds missing a structural feature necessary for PPAR activity would lead to compounds with PPAR activity. The appellants request that the Board make this determination before making an obviousness determination on the merits.

The differences between the prior art references and the claimed compounds. The two references and the claimed compounds are structurally distinct from each other and all have distinct biological properties.

Akiyoshi discloses two examples of compounds with an unsubstituted phenyl substituent corresponding to Ar^1 in the claimed genus (see structure above). Akiyoshi generically embraces only unsubstituted phenyl in that position (see translation, p.4, column 2, where R^2 lists "phenyl group"). The claimed genus differs in that Ar^1 mandates that the phenyl group must be substituted and cannot be unsubstituted (that is, R^4 on Ar^1 is a substituent other than hydrogen). The examiner is incorrect when she states that "Akiyoshi generically embrace the instant compounds."

Sierra discloses and claims compounds with a glycolic acid/ester moiety (see structure above). The glycolate moiety is present in 57 of 57 thiazole examples and therefore fairly teaches that this moiety is a necessary structural feature for this series of PPAR compounds. The claimed genus does not and cannot incorporate the glycolate moiety.

Therefore, the claimed genus differs from the prior art at least at Ar^1 and R^2 and R^3 (see structure below).



Additionally, the Akiyoshi compounds exhibit insecticidal activity while the Sierra compounds demonstrate PPAR activity. Therefore not only are the claimed compounds distinct—both in structure and in biological activity—but Akiyoshi and Sierra are also distinct from each other both in structure and in biological activity.

The level of skill in the art. The applicants believe the level of skill in the art is a medicinal chemist pursuing research in the area of potassium ion channels and note that the prior art references are not in ion channels but instead are in insecticidal and PPAR arts.

Prima facie case of obviousness. To establish a prima facie case, the examiner must show some motivation or suggestion to make the claimed compounds. *In re Brouwer*, 77 F.3d, 422, 425, 37 USPQ2d 1663 (Fed. Cir. 1996). For chemical compounds, structural similarity between claimed compounds and prior art compounds creates a prima facie case for obviousness where the prior art gives reason or motivation to make the claimed compounds. *In re Dillon* 919 F.2d 688 (Fed. Cir, 1991). The prior art does not need to render new utilities obvious. However, the prior art must provide enough structural similarity to render the claimed compounds obvious for prior known uses. *Id.* at 693. Therefore, under *Dillon*, the prima facie case must render the claimed compounds obvious for the previously disclosed utilities of insecticidal or PPAR activity.

The examiner argues that "Akiyoshi generically embraces the instant compounds." And relying on the principle that structurally similar compounds will exhibit similar properties, argues that "one having ordinary skill in the art would have found it prima facie obvious to select any of the compounds embraced by the generic formula."

First, as shown above, the claimed genus is distinct from Akiyoshi for the variable Ar^1. In the claimed genus Ar^1 can only be substituted phenyl; in Akiyoshi Ar^1 can only by unsubstituted phenyl. The examiner has not argued any reason for obviousness other than they are generically embraced. Thus, the examiner's argument that the claimed genus is obvious because it is generically embraced is incorrect.

Second, even if Akiyoshi embraced the claimed genus, that does not render subgeneric groups or species prima facie obvious. *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). Rather,

obviousness is a fact based inquiry and the examiner must offer objective teachings that render the subgenus obvious. The mere fact that the prior art can be modified to arrive at the claimed compounds is insufficient to establish a prima facie case of obviousness. *In re Fritch*, 972 F.2d 1266, 23 USPQ 1780 (Fed. Cir. 1992). The examiner cannot make the conclusory statement that the claimed compounds are similar. *In re Grabiak*, 769 F.2d 729, 226 USPQ 872 (Fed. Cir. 1985). *Grabiak* states that compounds with "very close" structural similarity and similar utilities may be prima facie obvious "without more." But *Grabiak* pointed out that the examiner is not free to decide what "very close" structural similarity is. The examiner must show support from the prior art:

> "there must be adequate support in the prior art for the ester/thioester change in structure in order to complete the prima facie case." *In re Grabiak*, 769 F.2d 729, 226 USPQ 872 (Fed. Cir. 1985).

See also *In re Dillon* where tri-orthoesters rendered tetra-orthoesters obvious because they were both disclosed in the prior art as behaving similar in chemical reactions. The examiner has offered no objective support that those in the insecticidal art would be lead from unsubstituted phenyl to any particular substituted phenyl substituent claimed by any teaching in the art.

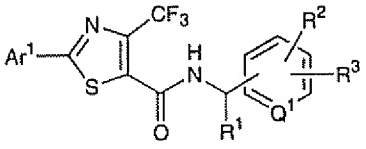
Third, the only way for the examiner to construe the claimed compounds to be within any generic structure is to selectively incorporate the substituted phenyl group of Sierra into the Akiyoshi genus while selectively declining to incorporate the glycolate moiety and totally ignoring the fact that the two references do not share any common property. The appellants argue that the references must considered in their entirety and the examiner cannot pick and choose what to incorporate and what to decline arbitrarily.

If read in their entirety, the references do not render the claimed compounds obvious. The references do not share any common property, therefore the principle that similar compounds will have similar activity is not applicable. The Akiyoshi reference must borrow the substituted phenyl for no objective reason other than to render the claimed genus within a fabricated generic scope of mixed biological activity.

The examiner has not provided any support that Akiyoshi should be combined with Sierra or that any prior art compound is similar in structure or in activity such that skilled artisans would be lead to compounds within the claimed genus. Akiyoshi and Sierra do not provide any motivation or suggestion to make the claimed compounds and therefore have not established a prima facie case of obviousness.

(viii) Claims appendix.

1. (previously presented) A compound of Formula I

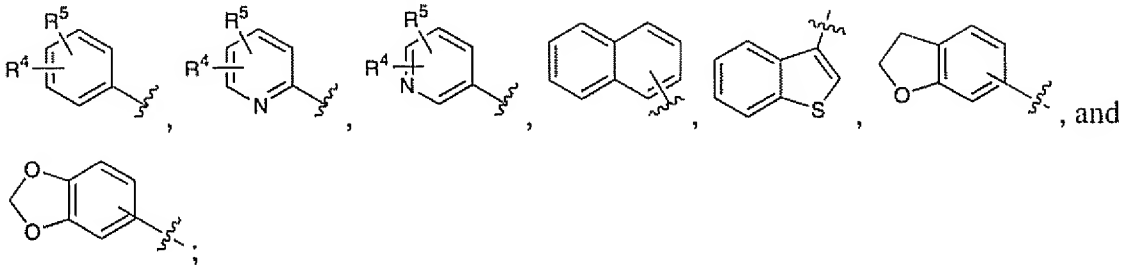


I

where:

Q^1 is CH;

Ar^1 is selected from the group consisting of

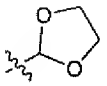


; and

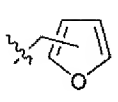
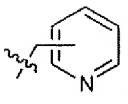
R^1 is hydrogen, C_{1-6}alkyl, hydroxymethyl, or trifluoromethyl;

R^2 is halogen, C_{1-6}alkyl, C_{1-2}perfluoroalkyl, C_{1-6}alkoxy, C_{1-2}perfluoroalkoxy, $-NR^6R^7$, $-(CH_2)_{1-4}NR^6R^7$, $-O(CH_2)_{2-3}NR^6R^7$, or pyridyl;

R^3 is hydrogen, halogen, or C_{1-6}alkoxy;

R^4 is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, $-NR^6R^7$, $-(CH_2)_{1-4}NR^6R^7$, $-O(CH_2)_{2-3}NR^6R^7$, or  ;

R^5 is hydrogen, halogen, or C_{1-6}alkoxy;

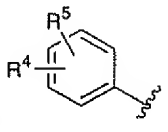
R^6 is hydrogen, C_{1-6}alkyl, -C(=NH)NH_2,  , or  ;

R^7 is hydrogen or C_{1-6}alkyl;

or R^6 and R^7 taken together are -$CH_2CH(CH_3)OCH(CH_3)CH_2$- or -$CH_2CH_2XCH_2CH_2$-, where X is a chemical bond, CH_2, CHOH, NH, NCH_3, $NCOCH_3$, O, or S;

or a pharmaceutically acceptable salt thereof.

2. (cancelled)

3. (original) A compound of claim 1 where Ar^1 is  .

4. (previously presented) A compound of claim 3 selected from the group consisting of

2-(4-fluorophenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-methoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-methoxyphenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(2-fluorophenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-fluorophenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(2-methoxyphenyl)-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3-methoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-[3-(dimethylamino)phenyl]ethyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-[3-(dimethylamino)phenyl]ethyl]-2-(2-fluorophenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(3-fluorophenyl)methyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(4-methoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3,4-dimethoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2,4-dimethoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2,4-dimethoxyphenyl)-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-methoxyphenyl)-N-[1-[3-(1-piperidinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-methoxyphenyl)-N-[1-[3-(1-pyrrolidinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-[3-[(2-furanylmethyl)methylamino]phenyl]ethyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-fluorophenyl)-N-[1-[3-[(2-furanylmethyl)methylamino]phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3,4-dimethoxyphenyl)-N-[1-[3-(1-pyrrolidinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-fluorophenyl)-N-[1-[3-(4-morpholinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-(3-aminophenyl)ethyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-[3-[(aminoiminomethyl)amino]phenyl]ethyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-[3-(dimethylamino)phenyl]ethyl]-2-(5-fluoro-2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[(3-fluorophenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[(3-methoxyphenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(5-fluoro-2-methoxyphenyl)-N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-chlorophenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-chlorophenyl)-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-chlorophenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(2-chlorophenyl)-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(2-chlorophenyl)-N-[1-[3-(4-morpholinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[2-(diethylamino)ethoxy]phenyl]-N-[(3-fluorophenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-2-[2-(4-morpholinyl)phenyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(4-morpholinyl)phenyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-[2-(4-morpholinyl)phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[4-(4-morpholinyl)phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(dimethylamino)methyl]phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(dimethylamino)methyl]phenyl]-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(dimethylamino)methyl]phenyl]-N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[(3-fluorophenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(4-fluorophenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

N-[(3-fluorophenyl)methyl]-2-(3-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-(2,3-dihydro-5-benzofuranyl)ethyl]-2-(3-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3,4-dimethoxyphenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(3,4-dimethoxyphenyl)-N-[1-(3,4-dimethoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3,4-dimethoxyphenyl)-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3-fluorophenyl)-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(2,4-dimethoxyphenyl)-N-[(3-fluorophenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3-fluorophenyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-(3-bromophenyl)ethyl]-2-(2-methoxyphenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-(4-morpholinyl)phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-(4-morpholinyl)phenyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-2-[3-(4-morpholinyl)phenyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[2-(diethylamino)ethoxy]phenyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[2-(diethylamino)ethoxy]phenyl]-N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[1-(3-aminophenyl)ethyl]-2-(2-fluorophenyl)-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[2-(diethylamino)ethoxy]-5-fluorophenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(dimethylamino)methyl]phenyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[1-[3-(4-morpholinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(diethylamino)methyl]phenyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(4-morpholinylmethyl)phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(4-morpholinylmethyl)phenyl]-N-[[3-(trifluoromethoxy)phenyl]methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(4-morpholinylmethyl)phenyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3-fluorophenyl)-N-[(3-fluorophenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-2-[2-(4-morpholinylmethyl)phenyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-(3-methoxyphenyl)ethyl]-2-[2-[(4-methyl-1-piperazinyl)methyl]phenyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[(3-methoxyphenyl)methyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

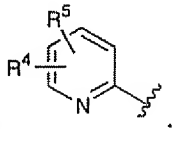
2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[1-[3-(4-morpholinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[ethyl(4-pyridinylmethyl)amino]methyl]phenyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)- 5-thiazolecarboxamide;

2-(2-methylbenzoyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide; and

N-[1-[4-fluoro-3-(4-morpholinyl)phenyl]ethyl]-2-(2-methylbenzoyl)-4-(trifluoromethyl)-5-thiazolecarboxamide.

5. (original) A compound of claim 1 where Ar^1 is 

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6. (original) A compound of claim 5 selected from the group consisting of

2-[3-[(diethylamino)methyl]-2-pyridinyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(4-pyridinylmethyl)amino]methyl]-2-pyridinyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(4-pyridinylmethyl)amino]methyl]-2-pyridinyl]-N-[1-[3-(4-morpholinylmethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-[3-[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]phenyl]ethyl]-2-[3-(4-morpholinylmethyl)-2-pyridinyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-[3-[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]phenyl]ethyl]-2-[3-[[ethyl(1-methylethyl)amino]methyl]-2-pyridinyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-[(1*S*)-1-[3-[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]phenyl]ethyl]-2-[3-[[ethyl(4-pyridinylmethyl)amino]methyl]-2-pyridinyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-(4-morpholinylmethyl)-2-pyridinyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(1-methylethyl)amino]methyl]-2-pyridinyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(4-pyridinylmethyl)amino]methyl]-2-pyridinyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(1-methylethyl)amino]methyl]-2-pyridinyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)- 5-thiazolecarboxamide;

2-[3-[(diethylamino)methyl]-2-pyridinyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-[3-[[ethyl(1-methylethyl)amino]methyl]-2-pyridinyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-(3-methyl-2-pyridinyl)-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-(3-methyl-2-pyridinyl)-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-(1,3-dioxolan-2-yl)-2-pyridinyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[3-[[ethyl(1-methylethyl)amino]methyl]-2-pyridinyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

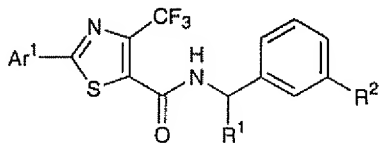
2-[3-[[ethyl(4-pyridinylmethyl)amino]methyl]-2-pyridinyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide; and

2-[3-(4-morpholinylmethyl)-2-pyridinyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide.

7. (original) A compound of claim 1 where R^1 is methyl.

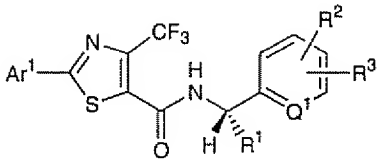
8. (original) A compound of claim 1 where R^1 is hydrogen.

9. (original) A compound of claim 1 where the structure is that of Formula Ig.



Ig

10. (original) A compound of claim 1 where R^1 is C_{1-6}alkyl and the stereochemical configuration is that of Formula Ia.



Ia

11. (original) A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

12. (withdrawn) A method for treating disorders responsive to opening KCNQ potassium channels comprising administering to a patient a therapeutically effective amount of a compound of claim 1.

13. (withdrawn) The method of claim 12 where the disorders are acute and chronic pain, migraine, neuropathic pain, bipolar disorders, convulsions, mania, epilepsy, anxiety, depression and neurodegenerative disorders.

14. (withdrawn) The method of claim 12 where the disorder is migraine.

15. (withdrawn) The method of claim 12 where the disorder is neuropathic pain.

16. (withdrawn) The method of claim 12 where the disorder is bipolar disorder.

17. (withdrawn) The method of claim 12 where the disorder is anxiety.

(ix) Evidence appendix.

None.

(x) Related proceedings appendix.

None.